UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,528	10/24/2003	Olaf Wilhelm	2923-576	7396

6449 7590 05/30/2007

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
05/30/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/691,528	WILHELM ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2007 and 06 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10-15* is/are allowed.

6)☒ Claim(s) *1-9 and 16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 6, 2007 has been entered.

Claims 1-19 are pending in the application and are being examined on the merits herein.

Applicants' arguments regarding the rejections of the claims under 35 U.S.C. 103(a) over Xing et al. in view of the Pentapharm product catalogs have been fully considered and have been found persuasive. In particular, Applicants have persuasively argued that one of ordinary skill in the art at the time the invention was made would not have found it obvious to provide the relatively *non-selective* urokinase inhibitor being claimed to treat tumors and metastases, as the state of the art at the time of filing of the application was such that only relatively *selective* urokinase inhibitors were considered to be suitable for the treatment of tumors and metastases.

Applicants have provided as evidence signed declarations by Dr. Foekens (Foekens declaration) and Dr. Cohen (Cohen declaration) demonstrating the state of the art regarding the use of urokinase inhibitors to treat tumors and metastases at the time of filing of the invention. The Cohen declaration states that the Pentapharm catalogs do not show the Pefabloc uPA inhibitor as a "selective" inhibitor of urokinase, and instead notes that it show a very low in vitro Ki value for both urokinase and plasmin, indicating a lack of selectivity for the urokinase over the plasmin (see paragraph 4 of Cohen declaration, in particular), and further states that Dr Cohen is of the opinion that the data shown in the Pentapharm catalogs does not show the desired degree of target selectivity (see paragraph 4 of Cohen declaration, in particular.) The Cohen declaration states that "it was a widely held scientific hypothesis and working principle of drug development in the area of metastasis that uPA inhibitors suitable for cancer therapy would need to have a high degree of specificity for inhibition of uPA (against tPA and plasmin)" (paragraph 4 of Cohen declaration), in order to avoid off-target effects such as unacceptable toxicity in the clotting system (see paragraph 4 of Cohen declaration.)

The Foekens declaration also states that the catalogs show in vitro results indicating a lack of selectivity of the particular compound, as the Ki values for trypsin, thrombin, Factor Xa, plasmin and sc-tPA are all relatively low and close to that of uPA (see paragraph 3, in particular.) As further evidence that those of ordinary skill in the art would not have been motivated to provide the compound having the activity profile as

shown in the catalogs to treat urokinase-associated diseases, the Foekens declaration points to the Towle et al. article "Inhibition of Urokinase by 4-substituted Benzo[b]thiophene-2-carboxamidines: An Important New Class of Selective Synthetic Urokinase Inhibitor" 1993, Cancer Research, Vol. 53, pages 2553-2559, as evidence of what was known to those of ordinary skill in the art at the time of filing regarding the necessary selectivity of urokinase inhibitors. Towle et al. discusses the use or urokinase inhibitors in the treatment of conditions involving cellular invasiveness, such as tumor metastasis (see paragraph bridging left and right hand columns of page 2553.) Towle et al. further teaches that urokinase inhibitors that also inhibit tPA are "unsuitable for use as antiinvasiveness drugs due to the potential undesired inhibition of tPA-mediated fibrinolysis" (right hand column of page 2553, first full paragraph, in particular.) Towle et al. also teaches that "similarly, antiinvasiveness uPA inhibitors should not inhibit plasmin, sice both uPA and tPA-mediated pathways converge through this enzyme. Unfortunately, such stringent selectivity requirements eliminate most of the known synthetic inhibitors of uPA" (right had column, first full paragraph, page 2553.) Thus, Towle et al. teaches that the lack of selectivity of known uPA inhibitors with regards to tPA and plasmin has been a long standing problem in the art, and has even eliminated uPA inhibitors from potential therapeutic use. Towle et al. also discloses that the uPA treatment agents taught by taught therein, B428 and B623, show a greater than 300 fold selectivity for uPA relative to tPA, and greater than 1000 fold selectivity for uPA relative to plasmin (see abstract of Towle et al.)

The Foekens declaration also notes that Towle et al. discloses that the IC_{50} values of amiloride for tPA and plasmin are at least 138 times greater than that for uPA and the IC50 value of B428 for tPA and plasmin are approximately 335 and 1100 times, greater than that for uPA (see Table 1 of Towle et al.) The Foekens declaration also notes that U.S. Patent No. 5,340,833 to Bridges reference discloses the importance of providing urokinase inhibitors with high selectivity with regards to other proteases such as tPA and plasmin, with suitable compounds being 60-800 fold more active at inhibiting uPA than tPA, and 400-10,000 fold more selective at inhibiting urokinase over plasmin (see column 10, lines 35-62 of Bridges.) In contrast, the Foekens declaration notes that the Ki values of the racemate compound for tPA and plasmin are only approximately 18 and 2 times, respectively, greater than that for uPA, and the Ki values for the L isomer are only 24 and 2-3 times, respectively, greater than that for uPA (see paragraph 9 of Foekens declaration.) Thus, the Foekens declaration concludes that the selectivity of the compound for uPA against tPA and plasmin is "not only very minimal in itself, but also quite insubstantial compared with those of amiloride or B428" (paragraph 9 of Foekens Declaration), and thus one of ordinary skill in the art would not have been motivated to provide the compounds described in the Pentapharm catalogs in the treatment of urokinase-associated disorders.

The Examiner finds these arguments persuasive. In particular, the Examiner notes that the state of the art as exemplified by Towle et al. and Bridges et al. appear to show that high selectivity of urokinase inhibitors was required in order to consider the

inhibitors for therapeutic use. The degree of selectivity of the compound with respect to tPA and plasmin appears to be minimal, particularly in view of the selectivity of suitable urokinase inhibitors as taught in the art by Towle et al. and Bridges et al. It is furthermore noted that Xing et al. clearly teaches the desirablility of providing *selective* inhibitors of urokinase (see abstract, in particular), and thus the Xing et al. reference also does not teach providing relatively nonspecific inhibitors such as the compound as claimed. Accordingly, the prior art as a whole shows that one of ordinary skill in the art would not have been motivated to provide a non-selective inhibitor of urokinase in the treatment of tumors or metastasis, as such a non-selective inhibitor would be expected to result in undesirable side effects that would negate any desirable effects achieved by the urokinase inhibiting action.

Accordingly, the rejection of claims 1-3, 5, 8-12, 15 and 18-19 under 35 U.S.C. 103(a) as being unpatentable over Xing et al. and the Pentapharm catalogs, as well as the rejection of claim 4 over Xing et al, Pentapharm and DeVita et al, the rejection of claims 6-7 and 13-14 over Xing et al, Pentapharm and U.S. Patent No. 5,736,129 to Medenica et al. and the rejection of claims 16-17 over Xing et al, Pentapharm and U.S. Patent No. 5,449,663 to Haim I. Bicher, are being withdrawn.

However, upon further consideration, the claims are being rejected as follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 16-19 are rejected under 35 U.S.C. 112, second paragraph, for lacking enablement for the full scope of the claims. The specification is enabling for a method of inhibiting urokinase *in vitro*, but is not enable for a method of inhibiting the growth and/or spreading of all urokinase associated malignant tumors, metastasis and/or lung foci, by administering the composition as claimed (Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanine 4-ethoxycarbonylpiperazide, the L enantiomer thereof or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.)

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set fourth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention: The instant invention pertains to method of inhibiting growth and/or spreading of any urokinase associated malignant tumors, metastases and/or lung foci, including both those known to be mediated by urokinase inhibition as well as any other tumors, metastases, etc. as well as those as-yet unknown.

2. The state of the prior art: The skilled artisan would view cancers, metastasis, tumors or lung foci as a group of maladies (cancers) not treatable with one medicament or therapeutic regimen. Treatment efforts and efforts to cure all tumors (cancers) have produced only isolated identifiable positive results. See *In re Application of Hozumi et al,* 226 USPQ 353. Moreover, it is well known that so far no single chemotherapeutic agent has been found to be useful in the treatment of **all** cancers, or even useful in the treatment of all types of tumors, such as all types of breast tumors, brain tumors, etc. For example, breast cancers and leukemia do not share a common cause and differ in their methods of treatment, i.e., breast cancers are routinely treated with estrogens, antiestrogens and/or androgens, unlike leukemia which is routinely treated with l-asparaginase, daunorubicin, and purine analogs.

Furthermore, according to Applicants own admission as to the state of the prior art, one of ordinary skill in the art would not have attempted to provide the compound as claimed for the treatment of urokinase disorders, because it was thought at the time of the invention that only those urokinase inhibitors that are *selective* inhibitors of urokinase over tPA and plasmin would be suitable for therapeutic use (see page 2 of Remarks submitted January 9, 2007 and declarations by Dr. Cohen and Dr. Foekens, in particular), whereas the instantly claimed compound is a *non-selective* inhibitor with regards to these proteases, as evidenced by the *in vitro* data shown in the Penthapharm 1997 and 1998 catalogs (of record.)

In particular, Applicants' cite the article "Inhibition of Urokinase by 4-substituted Benzo[b]thiophene-2-carboxamidines: An Important New Class of Selective Synthetic Urokinase Inhibitor" by Towle et al, 1993, Cancer Research, Vol. 53, pages 2553-2559, as evidence of what was known to those of ordinary skill in the art at the time of filing regarding the necessary selectivity of urokinase inhibitors. Towle et al. discusses the use or urokinase inhibitors in the treatment of conditions involving cellular invasiveness, such as tumor metastasis (see paragraph bridging left and right hand columns of page 2553.) Towle et al. further teaches that urokinase inhibitors that also inhibit tPA are "unsuitable for use as antiinvasiveness drugs due to the potential undesired inhibition of tPA-mediated fibrinolysis" (right hand column of page 2553, first full paragraph, in particular.) Towle et al. also teaches that "similarly, antiinvasiveness uPA inhibitors

should not inhibit plasmin, sice both uPA and tPA-mediated pathways converge through this enzyme. Unfortunately, such stringent selectivity requirements eliminate most of the known synthetic inhibitors of uPA" (right had column, first full paragraph, page 2553.) Thus, Towle et al. teaches that the lack of selectivity of known uPA inhibitors with regards to tPA and plasmin has been a long standing problem in the art, and has even eliminated uPA inhibitors from potential therapeutic use. Accordingly, by Applicants own admission, *non-selective* urokinase inhibitors such as that claimed were not considered to be suitable to provide treatment for urokinase-related disorders such as tumors, metastases, etc.

3. The predictability of the art, and the breadth of the claims: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 198 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Moreover, it is known that repeated therapeutic failures, after promising in-vitro results, suggest to the skilled artisan that claims based on in-vitro data, directed to treating cancer or tumors generally, are highly unpredictable, as taught in Trisha Gura's article in *Science*, November 1997 (of record):

"[T]he institute started by pulling together mouse models of three tumors: a leukemia, which affects blood cells; a sarcoma, which arise in bone, muscle, or connective tissue; and carcinoma, the most common cells and includes such major

killers as breast, colon, and lung cancers. Initially, many of the agents tested in these models appeared to do well. However, most worked against blood cancers such as leukemia and lymphoma, as opposed to the more common solid tumors. And when tested in human cancer patients, most of these compounds failed to live up to their early promise." (See first page, middle column.)

Based on the known teachings of the cancer treatment such as in Trisha Gura's reference, one of ordinary skill in the art would recognize that the treatment in the instant case, including the treatment of numerous and various potentially urokinase-associated tumors and cancers such as all urokinase-associated types of tumors, mestases and/or lung foci, with the very same compound, is highly unpredictable.

4. The presence or absence of working examples: the specification provides examples of *in vitro* inhibition of urokinase (see page 23, in particular), as well as examples of the treatment of the treatment of breast cancer in a rat breast cancer model with BN-472 breast cancer tumor fragments (see page 25, in particular), and in mice having human breast carcinoma cells MDA-BA-231 (see page 28, in particular), and the treatment of pancreatic carcinoma in a rat carcinoma model with pancreatic adenocarcinoma CA20948 (see page 26, in particular), and shows that treatment of the tumors was achieved as evidenced by reduction in weight of the tumors (see page 26, in particular) as well as a reduction in the number of lung foci seen in the breast tumor model, and a reduction in the number of liver foci in the pancreatic tumor model (see

page 27, in particular.) The specification also provides preclinical and phase I clinical in rat and mouse models supporting these results (see pages 31-36, note that preclinical and phase I clinical data not provided in parent applications.) However, as discussed by the article to Trisha Gura as discussed above, such treatment of cancers in rat or mouse models is not predictive of treatment of the same condition in human patients. The specification furthermore does not provide evidence or examples for the treatment of all urokinase associated malignant tumore, metastases and/or lung foci, as recited in the claim. Thus, the evidence in the examples is not commensurate in **scope** with the claimed invention.

Further, for those unknown or future known tumors, metastases and lung foci that are urokinase-associated, additional or future research would be required to discover and diagnose such conditions. Therefor, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Thus, the specification fails to provide sufficient support for the broad method of use of the claimed composition for treating numerous and various urokinase associated tumors, metastases and/or lung foci as recited in the instant claims. As a result, one of ordinary skill in the art would be required to perform an exhaustive search for the embodiments of the tumors, metastases and/or lung foci encompassed by the instant claims that can be treated by the compound as claimed, and that are thus suitable for the practice of the invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for a search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in *undue experimentation* to test all known and unknown urokinase associated tumors, metastases and/or lung foci encompassed by the instant claims, with no assurance of success.

Claims 1-9 and 16-19 under 35 U.S.C. 112, first paragraph, as not being enabling for the complete *inhibition*, i.e. prevention, of all urokinase associated malignant tumors, metastases and/or lung foci, as recited in the claim. Although the specification is enabling for the treatment of urokinase associated breast cancers and lung foci resulting from the metastases thereof, as well as pancreatic cancer and liver foci resulting from the metastates thereof, as has been discussed above, the specification is not enabling for the complete inhibition of such conditions, as required by the claim.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Foreman*, 230 USPQ 546 (Board of Appeals 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art: (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation that is necessary.

(1) *The Nature of the Invention:*

The invention is drawn to a method of *inhibiting*, i.e. preventing, all urokinase associated malignant tumors, metastases and/or lung foci, by administering the non-selective urokinase inhibitor as claimed.

(2) *Breadth of the Claims:*

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claimed invention includes the inhibition or prevention

of the tumors, metastases and lung foci as claimed. The term "inhibition" is being given its broadest reasonable interpretation as including complete "prevention" of the condition, and indicates a claim whereby those normally not at risk for developing such a disorder would be prevented from ever developing the disorder by administering the compound as claimed.

(3) ***Guidance of the Specification:***

The guidance of the specification as to "inhibition" or prevention of urokinase associated tumors, metastases and lung foci is completely lacking. As discussed above, the specification discloses examples of *in vitro* inhibition of urokinase, as well as the treatment of the treatment of breast cancer in a rat breast cancer model with BN-472 breast cancer tumor fragments (see page 25, in particular), and in mice having human breast carcinoma cells MDA-BA-231 (see page 28, in particular), and the treatment of pancreatic carcinoma in a rat carcinoma model with pancreatic adenocarcinoma CA20948 (see page 26, in particular), and shows that treatment of the tumors was achieved as evidenced by reduction in weight of the tumors (see page 26, in particular) as well as a reduction in the number of lung foci seen in the breast tumor model, and a reduction in the number of liver foci in the pancreatic tumor model (see page 27, in particular.) The specification also provides preclinical and phase I clinical data in rat and mouse models supporting these results (see pages 31-36, note that preclinical and phase I clinical data are not provided in parent applications.) Thus, while

the specification provides evidence of treatment in animal models, the specification does not provide evidence or examples for the complete inhibition, i.e prevention, of all urokinase associated malignant tumors, metastases and/or lung foci, as recited in the claim.

(4) *Working Examples:*

As discussed in the Guidance of the Specification section above, Applicant has only shown examples for the treatment of particular cancers in animal models with the compound as claimed. Applicant has not shown examples for the complete inhibition or *prevention* of urokinase associated malignant tumors, metastases and lung foci.

(5) *State of the Art:*

The state of the art regarding the *prevention* of cancers is underdeveloped. As discussed above, treatment efforts and efforts to cure all tumors (cancers) have produced only isolated identifiable positive results. See *In re Application of Hozumi et al,* 226 USPQ 353. Moreover, it is well known that so far no single chemotherapeutic agent has been found to be useful in the treatment of **all** cancers, or even useful in the treatment of all types of tumors, such as all types of breast tumors, brain tumors, etc. For example, breast cancers and leukemia do not share a common cause and differ in their methods of treatment, i.e., breast cancers are routinely treated with estrogens,

antiestrogens and/or androgens, unlike leukemia which is routinely treated with l-asparaginase, daunorubicin, and purine analogs.

It is furthermore noted that the article "The Urokinase-Type Plasminogen Activator System in Cancer Metastatis: A Review" by Andeasen et al, 1997, Int. J. Caner, Vol. 72, pages 1-22, teaches that while the urokinase-type plasminogen activator system is implicated in cancer metastasis, the exact interrelation of components of the system remains unknown (see abstract, in particular), and "a detailed knowledge of these processes is necessary for utilization of the therapeutic potential of interfering with the action of the system in cancers" (abstract.) Thus, the correlation amongst the various factors that are involved in the development of urokinase associated malignant tumors, metastases and lung foci, are not known.

Reasonable guidance with respect to *inhibiting* or *preventing* tumors, metastases and lung foci relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to the conditions. This type of data might be derived from widespread genetic analysis, family histories, correlation of genetic and environmental factors, etc. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of the tumor, metastasis or lung foci onset, and *link* those results with subsequent histological confirmation of the presence or absence of the tumors, metastasis and lung foci. This irrefutable link between antecedent drug and subsequent knowledge of the

prevention of the disease is the essence of a valid preventive agent. As the correlation among factors contributing to the development of tumors, metastases and lung foci is not known, the state of the art does not provide a reasonable method of making such a predictive analysis. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

(6) ***Predictability of the Art***

The invention is directed to the *inhibition* or *prevention* of urokinase associated tumors, metastases and/or lung foci in *general* with the compound as claimed. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *in re Fisher*, 427 F.2d 833, 839 (1970.)

It should also be noted that one of ordinary skill in the art would recognize that it is highly unpredictable in regard to what population will experience a malignant tumor, metastases and/or lung foci, as discussed in (5) above. In order to administer the agent to the population at large, one would need to consider the therapeutic effects, side effects and especially potential serious toxicity that may be generated by drug-drug interactions as a result of administration of the claimed compounds to a living organism (e.g., an animal.)

(7) *The Quantity of Experimentation Necessary:*

In order to practice the disclosed invention, one would need to undergo experimentation to test the compound to determine whether it is actually capable of completely preventing the development of malignant tumors, metastases and/or lung foci, as the instant specification does not show the complete prevention thereof.

As discussed above, the specification fails to provide sufficient support for determining all individuals susceptible to malignant tumors, metastases and/or lung foci to allow one or ordinary skill in the art to administer to a population the compound of the instant invention for the *inhibition* or *prevention* of the conditions in general. As a result, one of ordinary skill in the art would be forced to perform an exhaustive search for the population that is susceptible to the conditions to use the instant invention.

Genentech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The Examiner suggests deleting the reference to "inhibiting" in the claims.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been considered but are moot in view of the new grounds of rejection.

Allowable Subject Matter

Claims 10-15 are considered to be allowable over the prior art.

The claims are considered to be allowable because independent claim 10 recites a pharmaceutical composition comprising Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanin 4-ethoxycarbonylpiperazide, the L enantiomer thereof or a pharmaceutically acceptable salt thereof, and an additional, pharmacologically active substance, and a pharmaceutically acceptable carrier. Independent claim 15 recites a kit comprising the Nα(2,4,6-Triisopropylphenylsulfonyl)-3-amidino-(D,L)-phenylalanin 4-ethoxycarbonylpiperazide, the L enantiomer thereof or a pharmaceutically acceptable salt thereof, and radio labels and/or cytotoxic substances. The state of the prior art as taught by the Pentapharm 1997 and 1998 catalogs describes the compound as being an *in vitro* urokinase inhibitor. However, Applicants have persuasively argued that the *in vitro* urokinase selectivity shown in the catalogs would not be sufficient to motivate one of ordinary skill in the art to provide the compound generally in the treatment of

urokinase disorders. A general search of the prior art also does not reveal any other known therapeutic use for the claimed compound.

Accordingly, as the prior art does not teach any known therapeutic use for the compound as claimed, it is considered that one of ordinary skill in the art would not have been motivated to combine the claimed compound with a pharmacologically active substance, as recited in claim 10, let alone the radio labels and/or cytotoxic substances as recited in claim 15. Thus, these claims and the claims depending therefrom are considered to be allowable over the prior art.

Conclusion

Claims 10-15 are allowed, while claims 1-9 and 16-19 are rejected on new grounds.

The prior art made of record and not relied upon that is considered pertinent to Applicants' disclosure is cited in the accompanying PTO-892 form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER